REMARKS

A copy of a February 26, 2003 Associate Power of Attorney in the instant application that was granted to Kevin J. McGough by an attorney of record for the Applicants is attached herewith. Authorization is hereby given, and the Patent and Trademark Office is hereby requested, to charge Biogen Deposit Account 02-2327 for all fees required in connection with the filing of the instant Response. If, for whatever reason, the Patent and Trademark Office will not charge those fees to Biogen Deposit Account 02-2327, authorization is hereby given to charge the fees in the alternative to Coleman, Sudol & Sapone Deposit Account 04-0838.

Applicants respectfully request that future communications in connection with the instant application be addressed to Mr. McGough care of Coleman, Sudol & Sapone at the address provided below. Mr. McGough's office phone number is 914-337-4082.

Consistent with the April 11, 2003 telephone conference between Applicants' undersigned counsel and Examiner Haddad, the specification has been amended to note that Figure 15 illustrates the amino acid sequence of the human α1-I integrin polypeptide sequence. The amino acid sequence of the epitope for the anti-α1-I domain blocking mAbs (SEQ ID NO:8) comprises amino acids 91-96 in the box in Figure 15. The specification has been amended to note that an α1β1 function blocking antibody as used herein refers to an antibody that binds to the α1-I domain, specifically at an epitope identified by amino acids 91-96 of Figure 15, and that blocks α1β1 function as tested for, by example, the ability to inhibit K562- α1 dependent adhesion to Collagen IV (see Example 15). Claim 1 has been amended to note that the epitope comprises amino acid residues 91-96 of Figure 15 (SEQ ID NO:8). Corrected figures shall be submitted upon issuance of a Notice of Allowance.

Support for all of these amendments is found in the application as originally filed at page 9, lines 9-13; page 36, lines 3-5; in the amino acid sequence of the epitope found at page 2, line 6; and in the sequence listings SEQ ID NOS 6 and 8 filed with the original application.

It is respectfully submitted that these amendments overcome the objections to the claims and the specification noted in the Office Action.

Claim Rejections: 35 U.S.C. § 102(e)

Claims 1-6 were rejected under 35 U.S.C. § 102(e)("Section 102(e)") as being anticipated by U. S. Patent No. 5,788,966 ("*Chess*"). According to the examiner, *Chess* teaches the use of the same "product" as the methods of claims 1-6, and discloses that the mAb 1B3.1 inhibits collagen binding to VLA-1 and recognizes an epitope on VLA-1. The examiner asserts that function blocking is inherent in *Chess*. Applicants respectfully submit that this rejection is improper and should be withdrawn.

Chess discloses that mAb 1B3.1 "reacts with T cells which have been activated for prolonged periods, both *in vitro* and *in vivo*." *Chess; col. 7, lines 52-54.* The reference discloses that the VLA-1 molecule may participate in the compartmentalization of activated T cells to sites of tissue localized immune responses such as those occurring in the synovia. *Col. 9, lines 3-6.* And Chess notes that the synovial fluid of arthritis patients expresses enhanced levels of VLA-1. *Col. 8, lines 67-68.* There is no disclosure in *Chess* of mAb binding to an epitope of VLA-1 comprising amino acid residues 91-96 of Figure 15 (SEQ ID NO:8) to provide a decrease in arthritic score of about 65% or greater when compared to a control antibody treated subject. *Chess's* disclosure that mAb 1B3.1 affects the interaction of VLA-1 and T cells in conditions where enhanced levels of VLA-1 are noted does not disclose binding of mAb's to an epitope of VLA-1 comprising amino acid residues 91-96 of Figure 15 (SEQ ID NO:8) to provide a decrease in arthritic score of about 65% or greater when compared to a control antibody treated subject.

On these facts, the burden is not on the Applicants to show that *Chess's* mAb 1B3.1 could not under any circumstances target amino acid residues 91-96 of Figure 15 (SEQ ID NO:8) to provide a decrease in arthritic score of about 65% or greater when compared to a control antibody treated subject. Rather, the burden is on the Examiner to establish that *Chess* in fact enables that claimed method. To anticipate

under Section 102, a prior art reference must disclose each and every limitation of the claimed invention, must be enabling, and must describe the claimed invention sufficiently to have placed it in the possession of a person of ordinary skill in the field of the invention." *Helifix Ltd. v. Blok-Lok, Ltd., 54 U.S.P.Q.2d 1299 (Fed. Cir. 2000).* *Chess* does not specifically describe mAb's that target amino acid residues 91-96 of Figure 15 (SEQ ID NO:8) in the treatment of arthritis to obtain the clinical endpoint of a decrease in arthritic score of about 65% or greater when compared to a control antibody treated subject.

Further, Applicants have not merely defined advantageous clinical end points within a treatment regimen specified by *Chess*. Instead, the invention of the pending claims utilizes mAb's that target amino acid residues 91-96 of Figure 15 (SEQ ID NO:8) in the treatment of arthritis to obtain the clinical endpoint of a decrease in arthritic score of about 65% or greater when compared to a control antibody treated subject. There is no inherent anticipation in this instance. *See Rapoport v. Dement, et al., 59 U.S.P.Q. 2d 1215 (Fed. Cir. 2001).* *Cf. Bristol Myers Squibb Co. v. Ben Venue Laboratories, Inc., et al 58 U.S.P.Q. 2d 1508, (Fed. Cir. 2001).* Applicants have provided a novel method of treatment that is patentably distinguishable from *Chess's* disclosure that mAb 1B3.1 reacts with T cells which have been activated for prolonged periods, both *in vitro* and *in vivo*.

Claim Rejections: 35 U.S.C. § 103

Claims 1-7 have been rejected as obvious over *Chess* in light of *Riikonen* and *Fabbri*. Per the Examiner, it would have been obvious to those of ordinary skill in the art to substitute *Chess's* 1B3.1 mAb with *Fabbri's* mAb FB12 to treat rheumatoid arthritis. The Examiner supports this assertion by combining *Riikonen's* observation that $\alpha 1\beta 1$ expression is seen in the synovial lymphocytes of patients with rheumatoid arthritis with *Fabbri's* disclosure that the FB12 mAb binds to ECM, which, according to *Riikonen*, is found in the synovial lymphocytes of patients with rheumatoid arthritis.

Riikonen discloses that the mAb SR-84 blocks the function of $\alpha 1\beta 1$ integrin and that in HeLa cells $\alpha 1\beta 1$ integrin acts as a receptor for certain types of collagen. The

experimental results disclosed in *Riikonen* are said to be consistent with earlier findings that α1β1 can mediate cell adhesion to laminen-1 but not to fibronectin. *Riikonen, p. 209.*

Fabbri discloses that the FB12 mAb is functional in that it blocks the adhesion of activated T lymphocytes to fibronectin, collagen type IV and laminin.
Fabbri concludes that the FB12 mAb "may represent a useful reagent for the study of the biological function of α1-1 integrin I domain" and also states that the disclosed results "suggest that the α1-1 domain has a functional role in lymphocyte binding to ECM proteins, including FN." *Fabbri, p. 50.*

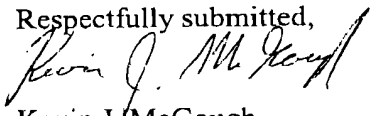
Chess, Riikonen or *Fabbri* do not disclose that the FB12 mAb will bind to an epitope of VLA-1 comprising amino acid residues 91-96 of Figure 15 (SEQ ID NO:8) to provide a decrease in arthritic score of about 65% or greater when compared to a control antibody treated subject. Viewed collectively, *Chess's* description of mAb 1B3.1 reactions with T cells, *Fabbri's* disclosure that the FB12 mAb blocks adhesion of activated T lymphocytes to fibronectin, and *Riikonen's* discloses that the mAb SR-84 blocks the function of α1β1 integrin (which can act as a receptor for certain types of collagen) describe the behavior of three different mAbs under different experimental conditions. Whether taken individually or in combination, those references do not specify the use of mAb's that target amino acid residues 91-96 of Figure 15 (SEQ ID NO:8) in the treatment of arthritis to obtain the clinical endpoint of a decrease in arthritic score of about 65% or greater when compared to a control antibody treated subject.

If the alleged obviousness of a claimed invention is based on a combination of references, there must be a rigorous showing of a clear and particular suggestion, teaching, or motivation to combine the references relied upon. *In Re Dembiczak, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999).* Such evidence may come from the references themselves, the knowledge of those skilled in the art, or from the nature of the problem to be solved. While this showing may come from the prior art, as filtered through the knowledge of one skilled in the art, *Brown and Williamson Tobacco Corp., Inc. v. Philip Morris Inc., 56 U.S.P.Q. 2d 1456 (Fed. Cir. 2000)*, it is still subject to the rigorous requirement that the combination not be motivated by impermissible hindsight. *In Re*

Dembiczak, supra. Further, there must be a particular showing that one of ordinary skill in the art would have believed there was a reasonable likelihood of success that the suggested combination of references would work to yield the claimed invention. *Brown and Williamson Tobacco Corp, supra.* The Examiner has failed to provide a rigorous showing of a clear and particular suggestion, teaching, or motivation to combine *Chess, Fabbri*, and *Riikonen* to yield the methods of claims 1-7.

In light of all of the foregoing, it is respectfully maintained that each of the claims are in a condition for allowance and that the Examiner should withdraw all of his outstanding grounds for rejection. Accordingly, Applicants respectfully request that claims 1-7 be passed to issue.

Respectfully submitted,



Kevin J. McGough
Reg. No. 31,279
Attorney for the Applicants
914-337-4082 (Office Number)

Of Counsel-Coleman, Sudol & Sapone
714 Colorado Avenue
Bridgeport, CT 06605-1601
(203) 366-3560
Date: April 21, 2003

Version Showing Mark-ups

In the Specification:

On page 2, lines 1-6, please amend the paragraph as follows:

[More particularly, the invention provides a method for the treatment of an inflammatory disorder in a subject comprising administering to the subject a pharmaceutical composition comprising an effective amount of an α1β1 function blocking antibody or a fragment of the antibody, wherein the α1β1 function blocking antibody or fragment is capable of binding an epitope of VLA-1 comprising amino acid residues 92-97, Val-Gln-Arh-Gly-Gly-Arg.] More particularly, the invention provides a method for the treatment of an inflammatory disorder in a subject comprising administering to the subject a pharmaceutical composition comprising an effective amount of an α1β1 function blocking antibody or a fragment of the antibody, wherein the α1β1 function blocking antibody or fragment is capable of binding an epitope of VLA-1 comprising amino acid residues 91-96, Val-Gln-Arg-Gly-Gly-Arg.

On page 6, line 11, please amend the sentence as follows.

[Figure 15. Amino acid sequence of the α1-I domain.] Figure 15. Figure 15 illustrates the amino acid sequence of the human α1-I integrin polypeptide sequence. The amino acid sequence of the epitope for the anti-α1-I domain blocking mAbs (SEQ ID NO:8) is shown in the box.

On page 9, line 19, please amend the sentence as follows.

[An α1β1 function blocking antibody as used herein refers to an antibody that binds to the α1-I domain, specifically, residues 92-97 of Figure 15, and that blocks α1β1 function as tested for, by example, their ability to inhibit K562- α1 dependent adhesion to Collagen IV (see Example 15).]

An α1β1 function blocking antibody as used herein refers to an antibody that binds to the α1-I domain, specifically at an epitope identified by amino acids 91-96 of Figure 15, and that blocks α1β1 function as tested for, by example, the ability to inhibit K562- α1 dependent adhesion to Collagen IV (see Example 15).

In the Claims

Amend claim 1 as follows:

--1. (Once amended) A method for the treatment of arthritis comprising administering to a subject suffering from arthritis a composition comprising a function blocking antibody or a fragment of said antibody, capable of binding an epitope of VLA-1 wherein the epitope comprises amino acid residues [92-97] 91-96 of Figure 15(SEQ ID NO:8), and in an amount effective to provide a decrease in arthritic score of about 65% or greater when compared to a control antibody treated subject.--